Paper No. 57

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte CARL-HENRIK HELDIN, CHRISTER BETSHOLTZ, BENGT WESTERMARK, TIMOTHY J. KNOTT, JAMES SCOTT, and GRAEME I. BELL

Appeal No. 2002-0424
Application No. 08/453,350

ON BRIEF

Before WINTERS, GRIMES, and GREEN, Administrative Patent Judges.

GREEN, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 25-27, 43-45, and 55-66. Claims 46-54 are also pending but were withdrawn from consideration. See Paper No. 31, mailed July 8, 1997.

Claims 25-27 are representative of the claims on appeal and read as follows:

> 25. A recombinant protein preparation comprising a PDGF A-chain homodimer comprised of two disulfide linked chains, each of said chains comprising the amino acid sequence numbered 87-193, inclusive, of Figure 1, or an analog of said sequence that comprises

less than 10 amino acid variations and retains PDGF biological activity as measured using a human foreskin fibroblast mitogen assay, wherein said protein preparation is produced in a nonhuman cell such that said protein preparation is free of other human proteins.

26. A recombinant protein preparation comprising a PDGF A-chain homodimer comprised of two disulfide linked chains, each of said chains comprising (a) the amino acid sequence numbered 87-196, inclusive, of Figure 1, (b) the amino acid sequence numbered 87 to 196, inclusive, of figure 2, or (c) an analog of (a) or (b) that comprises less than 10 amino acid variations and retains PDGF biological activity as measured using a human foreskin fibroblast mitogen assay, wherein said protein preparation is produced in a nonhuman cell such that said protein preparation is free of other human proteins.

27. A recombinant protein preparation comprising a PDGF A-chain homodimer comprised of two disulfide linked chains, each of said chains comprising the amino acid sequence numbered 87-211, inclusive, of Figure 1, or an analog of said sequence that comprises less than 10 amino acid variations and retains PDGF biological activity as measured using a human foreskin fibroblast mitogen assay, wherein said protein preparation is produced in a nonhuman cell such that said protein preparation is free of other human proteins.

The examiner relies on the following reference:

Heldin et al. (Heldin), "A human osteosarcoma cell line secretes a growth factor structurally related to a homodimer of PDGF A-chains," Nature, Vol. 319, pp. 511-514 (1986)

Claims 25-27, 43-45, and 55-66 stand rejected under 35 U.S.C. § 102(b) as anticipated by Heldin.

Claims 55-57 also stand rejected under 35 U.S.C. § 103 as obvious in view of Heldin.

We reverse both rejections.

Background

Platelet-derived growth factor (PDGF) is "a potent chemoattractant for monocytes and neutrophils and for fibroblasts and smooth muscle cells. These activities make PDGF an important component in tissue repair processes." Specification, page 1. "Purified native PDGF is a glycoprotein of approximately 30,000 daltons and is composed of two disulfide-linked chains. There are two types of chains, designated A and B. Whether native PDGF is a heterodimer, a mixture of homodimers, or a mixture of heterodimer and homodimer(s) is not known, but the dimer structure is functionally important, since reduction irreversibly destroys the biological activity of PDGF." Id., page 2.

The specification discloses "the isolation of cDNAs encoding two forms of PDGF A-chain precursors." Page 3. The cDNAs encode amino acids 1-196 and 1-211 of the PDGF A-chain; mature PDGF A-chain consists of amino acids 87-193. See the specification, pages 6-7. The specification also discloses that the cloned cDNAs can be expressed in a variety of host cells (pages 8-12), and exemplifies expression in CHO cells and yeast (pages 18-34).

Discussion

Claim 25 is directed to a protein preparation comprising a PDGF A-chain homodimer, where each of the two chains comprise amino acids 87-193 of the sequence shown in the application's Figure 1 (or an active analog having less than 10 amino acid variations), "wherein said protein preparation is produced in a nonhuman cell such that said protein preparation is free of other human proteins." Claims 26 and 27 are similar, except that the homodimer in the

claimed preparation comprises amino acids 87-196 and 87-211, respectively, of the PDGF A-chain.

The examiner rejected all of the claims as anticipated by Heldin, on the basis that "Heldin teaches a PDGF AA homodimer (ODGF) derived from osteosarcoma cells." Examiner's Answer, page 4. The examiner noted that the N-terminal amino acid sequence of Heldin's ODGF was identical to the PDGF A-chain and that Heldin's ODGF had PDGF agonist activity and was bound by anti-PDGF antibodies. See id. With respect to the "free of other human proteins" limitation, the examiner noted that Heldin's data showed only a single band (ODGF) following SDS/PAGE and silver staining, and amino acid sequencing showed only a single sequence. Id.

Appellants submitted evidence intended to rebut the examiner's position. Among other evidence, Appellants filed declarations under 37 CFR § 1.132 by Christer Betsholtz and Lawrence Scott Cousens. Dr. Betsholtz stated that

> the methods described in Heldin would not produce ODGF preparations completely free of other human proteins. In particular, ODGF was isolated using a Sephacryl S-200 column, followed by a BioGel P-150 column, and then an HPLC RP8 column. The products of each of these methods would inherently include at least small amounts of human proteins other than human ODGF since the ODGF was isolated from human osteosarcoma cells. The methods for purifying proteins from human sources described above, cannot result in a protein product free of contaminating human proteins. . . .
>
> Recombinant methods of producing human PDGF A-chain, such as those described in the subject application, on the other hand, result in a preparation free of other human proteins. . . . This is because the only human structural gene present in the recombinant plasmids is the gene encoding human PDGF.

Betsholtz declaration, ¶¶ 5-6.

Dr. Cousens stated that

> It is well known in the field of protein chemistry that no purification technique that uses a human cell as the source of the protein, can render a preparation which is absolutely homogeneous and lacking in other human proteins. This is because no protein purification technique is capable of providing a completely pure product.

Cousens declaration, ¶ 3. A research article submitted with the Cousens declaration supported Dr. Cousens' position. Dr. Cousens also stated that the silver-staining and amino acid sequencing results disclosed by Heldin did not prove that the ODGF preparation was homogeneous. See ¶¶ 4 and 6:

> [T]he limits of detection or sensitivity of silver-stained gels varies greatly from protein to protein. In fact it is well known that a number of proteins which stain well with Coomassie blue, do not stain at all with silver stains! . . . Further, some low molecular weight proteins may diffuse out of the gel and not be stained at all, some may stain very weakly, and others may stain disproportionately strongly. . . . Thus, a single band on a silver-stained SDS polyacrylamide gel, as used in Heldin, does not prove that the product is homogeneous. . . .
>
> Finally, the fact that no other amino acid sequence was obtained from the Heldin preparation does not mean that other human contaminants were absent. For example, N-terminal sequencing will not detect contaminants with "blocked" amino termini and many eukaryotic proteins, including some human proteins, are blocked.

Appellants argue that the declaratory evidence shows that the product disclosed by the prior art differs from the claimed product, and therefore does not anticipate the claims. See, e.g., the Appeal Brief, pages 18-19.

"It is well settled that a claim is anticipated if each and every limitation is found either expressly or inherently in a single prior art reference." Celeritas Techs. Ltd. v. Rockwell Int'l Corp., 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522 (Fed. Cir. 1998). The initial burden, however, is on the examiner to show that the

claimed invention is not novel: "[I]n an ex parte proceeding to obtain a patent . . . the Patent Office has the initial burden of coming forward with some sort of evidence tending to disprove novelty." In re Wilder, 429 F.2d 447, 450, 166 USPQ 545, 548 (CCPA 1970).

The examiner may reject a claimed product as anticipated, even if the prior art does not disclose every limitation recited in the claims, if there is a reasonable basis for concluding that the limitations that are not expressly disclosed would have been present nonetheless. See, e.g., In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977) ("[I]t is elementary that the mere recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not cause a claim drawn to those things to distinguish over the prior art. Additionally, where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on.").

Here, we agree with the examiner that Heldin's disclosure was sufficient to support a conclusion that the prior art product was the same as the claimed product. Thus, the burden of proof was properly shifted to Appellants to show that the products were different. See In re Spada, 911 F.2d 705, 708, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). "In response to the PTO's asserted prima facie case the applicant may argue that the inference of lack of novelty was not properly drawn, for example if the PTO did not correctly apply or understand the

subject matter of the reference, or if the PTO drew unwarranted conclusions therefrom." Id.

After rebuttal evidence is submitted, the examiner must re-evaluate the basis of the rejection in light of all the evidence of record. Cf. In re Rinehart, 531 F.2d 1048, 1052, 189 USPQ 143, 147 (CCPA 1976): "When prima facie obviousness is established and evidence is submitted in rebuttal, the decision-maker must start over. . . . Prima facie obviousness is a legal conclusion, not a fact. Facts established by rebuttal evidence must be evaluated along with the facts on which the earlier conclusion was reached, not against the conclusion itself. Though the tribunal must begin anew, a final finding of obviousness may of course be reached, but such finding will rest upon evaluation of all facts in evidence, uninfluenced by any earlier conclusion reached . . . upon a different record."

Just as a prima facie case of obviousness must be re-evaluated in light of rebuttal evidence, so must a prima facie case of anticipation. The rejection may be maintained only if it is supported by a preponderance of the evidence in the record. See In re Caveney, 761 F.2d 671, 674, 226 USPQ 1, 3 (Fed. Cir. 1985) ("[P]reponderance of the evidence is the standard that must be met by the PTO in making rejections.").

In this case, Appellants submitted evidence showing that the prior art product could not have the properties recited in the instant claims. In particular, Appellants' evidence shows that the prior art preparation could not have been "free of other human proteins," as required by the claims. The examiner

dismissed Appellants' evidence, for several reasons. First, the examiner noted that Appellants had not "offered any comparative evidence to support [their] conclusion." Examiner's Answer, page 8. See also page 9: "[W]hen a prior art product reasonably appears to be the same as the claimed [product], but differs by [the] process in which it was produced, . . . the burden is upon Appellants to prove, by comparative evidence, a patentable difference."

We do not agree with this position. Comparative evidence is not the only type of evidence an applicant can rely on to show that a claimed product differs from those in the prior art. Any type of evidence can be used, as long as it persuasively shows that the claimed and prior art products differ. In this case, Appellants have provided declaratory evidence, supported by scientific articles, showing that a protein preparation purified from human cells will invariably contain other human proteins. See the Betsholtz declaration, the Cousens declaration, and the Kornberg article attached thereto. We find that Appellants' evidence persuasively shows that the protein preparation disclosed by Heldin does not meet the limitations of the instant claims.

The examiner also faulted Appellants for failing to define the term "free of other human proteins." See the Examiner's Answer, page 11:

> [T]he instant specification does not define "free of other human proteins." Since the claims do not recite free of all other human proteins, . . . this recitation does not encompass [sic, require?] absolute purity. Since the claims do not encompass [sic, require?] absolute purity, the preparation by Heldin meets the limitations of the claims. If the claims intend absolute purity, it is asserted that the claims are not enabled, because the preparation of a protein from a recombinant cell requires manipulation by a technician,

> which would ultimately result in contamination, which would not equate to absolute purity.

We do not find this reasoning persuasive. First, the examiner has not rejected the claims as indefinite; therefore, it appears that she has concluded that those skilled in the art know what is meant by "free of other human proteins." Nor has the examiner rejected the claims as nonenabled, or offered any evidence to support her assertion that protein preparations cannot be made completely free of contaminating human proteins. In particular, the examiner has offered no evidence or scientific reasoning to show that protein preparations made as disclosed in the instant specification would not be "free of other human proteins," as that term is understood by persons skilled in the art.

Appellants, on the other hand, have offered persuasive evidence that protein preparations made as disclosed by Heldin would not be "free of other human proteins." Thus, Appellants have carried their burden of rebutting the examiner's prima facie case of anticipation. The rejection under 35 U.S.C. § 102(b) is reversed.

The examiner also rejected claims 55-57 as obvious in view of Heldin. The § 103 rejection, however, relied on the same basic reasoning as the § 102(b) rejection. See the Examiner's Answer, page 5. Our reversal of the § 102(b) rejection therefore mandates reversal of the § 103 rejection, for the reasons discussed above.

Other Issues

Claims 61-63 depend on claims 26-28, respectively, but claim 28 has been canceled. It appears that claims 61-63 should depend instead on claims 25-27, respectively. Appellants and the examiner may wish to review the dependency of claims 61-63.

Summary

The examiner's rejections are not supported by a preponderance of the evidence in the record, and therefore must be reversed.

REVERSED

Sherman D. Winters)
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